DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration; ORA OPQO HQ 12420 Parklawn Drive, Room 2032 Rockville, MD 20857 email: ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	2/28/2022 to 3/04/2022
	FEI NUMBER 3010972581

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Yongjun Tu, CEO & Chairman of the Board

FIRM NAME	STREET ADDRESS
Zhejiang Tianyu Pharmaceutical Co. Ltd.	Jiangkou Development Zone, Huangyan,
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Taizhou City, Zhejiang 318020, China	API Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION 1 (Quality System)

Your firm failed to extend investigations to other batches that may have been associated with a specific failure or deviation,

Specifically,

On July 2020, your firm received a notification from one of your customers, requesting your firm to evaluate the possibility your process may produce [(b)(4)]. In your firm's investigation, it was identified that [(b)(4)] impurity is present in [(b)(4)] API in amounts higher than the specification establish by your firm of [(b)(4)] ppm. Your firm confirmed that at least three (3) batches of API were over [(b)(4)] ppm for [(b)(4)] Those batches were potentially used and distributed in finished dosage forms for the US market. In addition, your firm established in your investigation that the manufacturing process of the API previous to August 2018 had higher risk of producing [(b)(4)] as a by-product of your manufacturing process, however, your firm did not extend the investigation to those batches. Approximately [(b)(4)] batches manufactured on 2018 were sold for potential introduction in the US market.

OBSERVATION 2 (Quality System)

There is a failure to thoroughly review any unexplained discrepancy or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has been already distributed. Specifically,

Procedures for control of [(b)(4)] impurity evaluation during API process development establishes that [(b)(4)] impurity evaluation should be conducted before or after synthesis route is selected or confirmed. The procedure establishes that reagents, synthesis, reactions and by-products of starting material, intermediate, final product are to be evaluated for [(b)(4)] impurity.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
		Marcus Ray, Consumer Safety Officer Laurimer Kuilan-Torres, Consumer Safety Officer Dennis Cantellops, Consumer Safety Officer	3/04/2022

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a) Your firm did not evaluate the possibility of (b) (4) impurity (b) (4) and (b) (4) in (b) (4) API which are a by-products of the (b) (4) of the (b) (4) The failure of your firm to conduct a thorough evaluation resulted in complaints from your customers that some batches did not meet the specification of (b) (4)

b) Your firm failed to identify (b) (4) as potential impurity of your process. After your firm was notify about the impurity, the testing of your batches confirm the presence of (b) (4) in amounts of (b) (4) ppm (specification (b) (4) ppm). This resulted on returns of over thirty (30) batches of (b) (4) API distributed for usage in finished dosage forms for the US market. From the returned batches, eleven (11) were not return entirely and appear to be used by your customers.

c) The initial risk assessment of (b) (4) approved on 09/23/2020, was not assessed for the potential carryover of impurities from the starting materials. (b) (4) Your firm has received at least one (1) complaint for the presence of (b) (4) between (b) (4) (manufacturing start date) and November 2021 (complaint date).

OBSERVATION 3 (Facilities and Equipment System)

Equipment and utensils are not cleaned or maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product. Specifically,

There is no assurance that your firm's production equipment is properly maintained in order to prevent it from becoming a potential source of contamination for the manufactured products from this equipment, for example;

a) Your firm failed to complete the cleaning validation studies previous to release and deliver (b) (4) batches of (b) (4) starting material to (b) (4)

b) According to SOP-49520-208, "Cleaning SOP of (b) (4) a deep clean should occur (b) (4) A review of your usage logbook identifies cleaning occurred on the following dates, outside of the specified time-frame:

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Date Cleaned [(b) (4)] Number of Days Between Previous Cleaning [(b) (4)]

c) [(b) (4)] identified as [(b) (4)] located in the Workshop # [(b) (4)] used for the synthesis of [(b) (4)] [(b) (4)] were observed with an apparent brownish rust like (rouge) spots on the top walls of the [(b) (4)] on product contact surface areas. In addition, layers of thick black spots are above the brownish rust like (rouge) spots around the walls of the [(b) (4)] on product contact surface areas.

d) SOP # SMP-EN-003: tilted "Equipment Maintenance Procedure"; V02; failed to include the [(b) (4)] (Example: using a [(b) (4)]) of the [(b) (4)] when rust (rouge) is identified during routine equipment maintenance.

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